original report

Prediction of Progression-Free Survival in Patients With Advanced, Well-Differentiated, Neuroendocrine Tumors Being Treated With a Somatostatin Analog: The GETNE-TRASGU Study

Alberto Carmona-Bayonas, MD, PhD[1]; Paula Jiménez-Fonseca, MD, PhD[2]; Ángela Lamarca, MD, PhD[3]; Jorge Barriuso, MD, PhD[3,4]; Ángel Castaño, MD, PhD[5]; Marta Benavent, MD, PhD[6]; Vicente Alonso, MD, PhD[7]; María del Carmen Riesco-Martínez, MD, PhD[8]; Teresa Alonso-Gordoa, MD[9]; Ana Custodio, MD, PhD[10]; Manuel Sánchez Cánovas, PhD[1]; Jorge Hernando Cubero, MD, PhD[11]; Carlos López, MD, PhD[12]; Adelaida Lacasta, MD, PhD[13]; Ana Fernández Montes, MD[14]; Mónica Marazuela, MD, PhD[15]; Guillermo Crespo, MD, PhD[16]; Pilar Escudero, MD, PhD[17]; José Ángel Diaz, MD, PhD[18]; Eduardo Feliciangeli, MD[19]; Javier Gallego, MD, PhD[20]; Marta Llanos, MD, PhD[21]; Ángel Segura, MD[22]; Felip Vilardell, MD, PhD[23]; Juan Carlos Percovich, MD[24]; Enrique Grande, MD, PhD[25]; Jaume Capdevila, MD, PhD[11]; Juan W. Valle, MD, FRCP[3,4]; and Rocío García-Carbonero, MD, PhD[26]

abstract

PURPOSE Somatostatin analogs (SSAs) are recommended for the first-line treatment of most patients with well-differentiated, gastroenteropancreatic (GEP) neuroendocrine tumors; however, benefit from treatment is heterogeneous. The aim of the current study was to develop and validate a progression-free survival (PFS) prediction model in SSA-treated patients.

PATIENTS AND METHODS We extracted data from the Spanish Group of Neuroendocrine and Endocrine Tumors Registry (R-GETNE). Patient eligibility criteria included GEP primary, Ki-67 of 20% or less, and first-line SSA monotherapy for advanced disease. An accelerated failure time model was developed to predict PFS, which was represented as a nomogram and an online calculator. The nomogram was externally validated in an independent series of consecutive eligible patients (The Christie NHS Foundation Trust, Manchester, United Kingdom).

RESULTS We recruited 535 patients (R-GETNE, n = 438; Manchester, n = 97). Median PFS and overall survival in the derivation cohort were 28.7 (95% CI, 23.8 to 31.1) and 85.9 months (95% CI, 71.5 to 96.7 months), respectively. Nine covariates significantly associated with PFS were primary tumor location, Ki-67 percentage, neutrophil-to-lymphocyte ratio, alkaline phosphatase, extent of liver involvement, presence of bone and peritoneal metastases, documented progression status, and the presence of symptoms when initiating SSA. The GETNE-TRASGU (Treated With Analog of Somatostatin in Gastroenteropancreatic and Unknown Primary NETs) model demonstrated suitable calibration, as well as fair discrimination ability with a C-index value of 0.714 (95% CI, 0.680 to 0.747) and 0.732 (95% CI, 0.658 to 0.806) in the derivation and validation series, respectively.

CONCLUSION The GETNE-TRASGU evidence-based prognostic tool stratifies patients with GEP neuroendocrine tumors receiving SSA treatment according to their estimated PFS. This nomogram may be useful when stratifying patients with neuroendocrine tumors in future trials. Furthermore, it could be a valuable tool for making treatment decisions in daily clinical practice.

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ASSOCIATED CONTENT

Data Supplement

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INTRODUCTION

Gastroenteropancreatic neuroendocrine tumors (GEP-NETs) are a heterogeneous group of neoplasms that follow a variable clinical course and are defined by the WHO 2010 classification into three subgroups on the basis of proliferation index[1]; however, within each category, cases with a different clinical and biologic behavior continue to coexist.[2]

Somatostatin analogs (SSAs) are currently the recommended first-line treatment of most patients who are diagnosed with advanced, well-differentiated GEP-NETs[3,4] as they provide prolonged progression-free survival (PFS) with an acceptable toxicity profile. PFS is often used as an outcome measure of patients with GEP-NETs because it is a surrogate variable for overall survival (OS).[5,6] Despite SSAs being the

treatment of choice for many patients with GEP-NET, benefit from treatment—in terms of PFS—is far from homogenous across the entire spectrum of SSA-treated GEP-NETs. Several observations support the need to develop robust multivariable models to predict PFS that are able to assist clinicians in treatment decisions and investigators in the design of new treatment strategies. The phase III CLARINET (Controlled Study of Lanreotide Antiproliferative Response in Neuroendocrine Tumors) and PROMID (Prospective, Randomized Study on the Effect of Octreotide LAR in the Control of Tumor Growth in Patients with Metastatic Neuroendocrine Midgut Tumors) trials demonstrated the antiproliferative effect of SSAs,[7-9] with striking differences observed in median PFS in both studies. Most participants in the PROMID trial had a low liver tumor load and a Ki-67 index of 2% or less (expected to be a population with less aggressive, slow-growing disease). Despite this, approximately 25% of participants assigned to SSA in this study experienced progression before 6 months, which indicated that treatment was insufficient in that subgroup. Unfortunately, it was difficult to further characterize this patient population in univariable survival analyses. In the CLARINET study, long-acting lanreotide (Somatuline Autogel; Ipsen, Paris, France) prolonged PFS compared with placebo. Despite prognosis being notably different depending on the site of the primary tumor, other predictors of increased benefit from treatment were not identified.[7] Multivariable analyses have established that liver tumor load, histologic grade, and the site of the primary tumor are predictive factors for PFS, thus contributing to prognosis and representing factors to account for when making treatment decisions.[10] However, these and other studies failed to factor in the additive effect of multiple covariates that converge in the course of GEP-NETs or were insufficient to make individual predictions of PFS.[9,10]

Other targeted therapies, including antiangiogenics or phosphatidylinositol 3-kinase/AKT/mammalian target of rapamycin pathway inhibitors, have been incorporated into the treatment armamentarium of GEP-NETs over the past decade, administered concurrently or sequentially with SSAs. However, the optimal sequence and timing for the administration of each of these alternative treatments is uncertain.[11,12] It is hoped that new agents in the pipeline, such as axitinib, surufatinib, lenvatinib, cabozantinib, and others, may continue to improve NET management.[13] Furthermore, recent progress that has been made in clarifying the molecular biology of pancreatic NETs—with the identification of mutated or altered gene expression in DAXX/ATRX, phosphatidylinositol 3-kinase/Akt/mammalian target of rapamycin, multiple endocrine neoplasia 1, and other pathways—has provided potential new candidates for targeted therapies.[14] In this context of expanding therapeutic options, a predictive tool of benefit from treatment with SSAs could be useful for selecting the most adequate treatment according to individual predicted benefit,[15] as it is already happening in other advanced tumors.[16,17] This model would also inform discussions with patients in daily practice and assist in the design of future clinical trials.

The current study aimed to develop and externally validate a predictive model of PFS in patients with advanced, well-differentiated GEP-NETs treated with SSAs alone. Furthermore, we investigated the dynamic, nonlinear effects of Ki-67 percentage in combination with patients' proinflammatory status on the basis of the neutrophil-to-lymphocyte ratio.

PATIENTS AND METHODS

Study Population and Design

The model was designed in a training cohort that included patients from the Spanish National Cancer Registry (R-GETNE; data cutoff date for analyses was December 2018), a hospital-based registry managed by the Spanish Group of Neuroendocrine and Endocrine Tumors (GETNE). This observational registry included consecutive patients who were diagnosed with GEP-NETs. Its design, characteristics, and quality criteria have been reported previously.[2,18,19]

Inclusion criteria for this substudy, GETNE-TRASGU (Treated With Analog of Somatostatin in Gastroenteropancreatic and Unknown Primary NETs) consisted of histologic diagnosis of GEP-NET (pancreas, GI, or unknown origin), advanced disease measurable by Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1 and monitored using computed tomography at least every 6 months until progression,[20] well-differentiated tumor per WHO 2010 classification with Ki-67 of 20% or less,[21] and SSA monotherapy as first-line treatment of advanced disease maintained until progression or toxicity. Eligibility criteria conform to the standard for SSA administration for antiproliferative purposes, in accordance with international clinical guidelines as well as with regulatory conditions and clinical practice. Patients who were initially treated with other systemic treatments or curative surgery for metastatic disease, or cases with poor documentation of clinical information were excluded. Sixty centers from across the country participated in R-GETNE, and data from a total of 3,971 registered patients were screened for eligibility with additional data quality check—double checking all variables of interest, monitoring for discrepancies and missing data, and using multiple filters and controls so as to minimize unjustified loss of data.

Results were externally validated in a separate cohort from The Christie NHS Foundation Trust (Manchester, United Kingdom), which included consecutive patients who met inclusion criteria and for whom all items included in the nomogram were available. Any patients with missing information, including blood results at the time of SSA initiation, were excluded.

All procedures followed were in accordance with the ethical standards of the responsible committee on human

TABLE 1. Baseline Patient Characteristics

Characteristic	TRASGU Training Cohort: R-GETNE (n = 438)	TRASGU Validation Cohort: Christie Hospital Cohort (n = 97)
Median age, years (range)	62 (26-89)	64 (26-86)
Sex, female	205 (46.8)	48 (49.4)
Median Ki-67, % (range)	4 (0-20)	2 (1-20)
Missing values	1	0
Median neutrophils (range)	3,800 (290-22,000)	4,100 (1,700-13,470)
Missing values	45	0
Median lymphocytes (range)	1,700 (110-26,400)	1,400 (300-3,400)
Missing values	56	0
Alkaline phosphatase		
Normal	272 (62.1)	67 (69.0)
1.1-2.5 ULN	90 (20.5)	23 (23.7)
> 2.5 ULN	40 (9.1)	7 (7.2)
Missing values	36 (8.2)	0
SSA		
Sandostatin LAR, mg	215 (49.1)	50 (51.5)
30	165 (77.7)	48 (96.0)
20	45 (20.9)	1 (2.0)
10	1 (0.4)	1 (2.0)
Missing values	3 (1.3)	0
Lanreotide Autogel, mg	223 (50.9)	47 (48.4)
120	186 (83.4)	45 (95.8)
90	24 (10.7)	1 (2.1)
60	10 (4.4)	1 (2.1)
Missing values	3 (1.3)	0
Primary tumor site		
Small intestine	174 (40.0)	67 (69.1)
Pancreas	166 (37.9)	11 (11.3)
Unknown	43 (9.8)	12 (12.3)
Rectum	22 (5.0)	3 (3.1)
Colon	19 (4.3)	4 (4.1)
Stomach	7 (1.6)	0
Appendix	6 (1.4)	0
Median time from diagnosis of metastasis to the beginning of SSA treatment, months (range)	2.0 (0-84)	2.9 (0.4-72.3)

(continued on following page)

research (institutional and national) and with the Helsinki Declaration of 1964 and later versions. Informed consent, if applicable depending on the participating institution, was obtained from all patients before they were included in the study.

Objectives and Variables of Interest

The main end point of this study was PFS, which was defined as the interval of time between commencing SSA therapy and tumor progression or all-cause mortality, censoring patients who were lost to follow-up. The aim of the study was to develop and externally validate a model enabling patients with GEP-NET to be stratified on the basis of the length of PFS. Candidate predictors were initially chosen after a review of the literature and consulting with GETNE experts. Demographic (age and sex), family (multiple endocrine neoplasia 1 and other familial syndromes), clinical (body mass index, Eastern Cooperative Oncology Group performance status, and comorbidities), documented progression status before initiating SSA (tumor progression, stable disease not documented or < 3 months, and stable disease for ≥ 3 months), tumor (uptake on scintigraphy with octreotide, clinical status at SSA treatment initiation, functionality, hepatic tumor burden, number of organs affected, and sites of metastases), histopathologic (Ki-67 percentage, histologic differentiation, primary tumor site), and laboratory (alkaline phosphatase, bilirubin, albumin, lactate dehydrogenase, chromogranin A, 5-hydroxyindoleacetic acid, neutrophil-lymphocyte ratio [NLR], hemoglobin, and platelets) variables were included.

Statistics

Time-varying, nonlinear effects were explored using survival analysis with generalized additive models,[22,23] represented as three-dimensional surfaces and contour maps. No data-driven method was used in the final selection of variables.[24] We performed a redundancy analysis with flexible parametric additive models to eliminate any covariate that could be predicted by the remaining variables. To examine PFS, we used a log-normal accelerated failure time (AFT) model, given the nonproportionality of hazards.[25] In AFT models, survival times are multiplied by a constant effect under this formulation such that the exponentiated coefficients, $\exp(\beta)$, are referred to as time ratios (TRs). A TR of more than 1 for the covariate implies that this slows or prolongs the time to event, whereas a TR of less than 1 indicates that an event is more likely to occur earlier. Thus, the regression coefficient of a binary predictor equal to log(0.5) means that the median of time to event is halved in its presence. Time was measured as a continuous variable and is expressed in months.

We checked the adequacy of the log-normal parametric model by computing the Kaplan-Meier estimate of the distribution of residuals against the theoretical Gaussian one. Nonlinear effects were modeled by restricted cubic splines. Variables with more than 20% missing data were

TABLE 1. Baseline Patient Characteristics (continued)

Characteristic	TRASGU Training Cohort: R-GETNE (n = 438)	TRASGU Validation Cohort: Christie Hospital Cohort (n = 97)
Documented progression status before SSA		
Tumor progression	179 (40.8)	11 (11.3)
Stable disease ND or < 3 months	216 (49.3)	80 (82.4)
Stable disease for ≥ 3 months	43 (9.8)	6 (6.1)
Functioning tumor	120 (27.3)	39 (40.2)
Metastasis site		
Liver	376 (85.8)	78 (80.4)
Lymph nodes	153 (34.9)	76 (78.3)
Peritoneum	85 (19.4)	21 (21.6)
Bone	38 (8.7)	12 (12.3)
Lung	24 (5.5)	8 (8.2)
Other	24 (5.5)	6 (6.1)
Median No. of organs involved (range)	1 (1-6)	2 (1-4)
Octreotide scan, performed	389 (88.8)	84 (86.7%)
Positive	353 (90.7)	78 (92.8%)

NOTE. Data are given as No. (%), unless otherwise noted.

Abbreviations: LAR, long-acting release; ND, not documented; R-GETNE, Spanish Group of Neuroendocrine and Endocrine Tumors Registry; SSA, somatostatin analog; TRASGU, Treated With Analog of Somatostatin in Gastroenteropancreatic and Unknown Primary Neuroendocrine Tumors; ULN, upper limit of normal.

eliminated—for example, mitosis, chromogranin A, and 5-hydroxyindoleacetic acid. Remaining missing data were then imputed by predictive mean matching.[26] The Data Supplement provides an at-a-glance plot of the pattern of missing data in the data set. Regarding sample size, the number of predictors was chosen so that there would be at least 15 events per covariate.[24] The model was represented as a nomogram; calibration curves were plotted and discrimination assessed using Harrell's C-index, which takes into account the right-censored data. Analyses were performed using R version 3.5.1,[27] including the Hmisc, rms, mgcv, visreg, and pammtools packages.[22,28-31]

RESULTS

Patients and Treatments

The final GETNE-TRASGU database contained 535 patients—438 from the R-GETNE training cohort and 97 from the external validation subset. Table 1 lists baseline characteristics of both subsets. Demographic data and therapies were similar in both cohorts, with the exception of a higher representation of small bowel primaries (69% *v* 40%) and a smaller proportion of tumors with confirmed progression status at the time of SSA initiation (11% *v* 40%) in the external validation cohort (*v* the R-GETNE training set). In the R-GETNE training cohort, a median of 21 doses of SSA were administered (range, one to 168 doses). Treatment was initiated at antiproliferative doses in 77% (octreotide long-acting release 30 mg every 4 weeks) and 83% (Lanreotide Autogel 120 mg every 4 weeks; Ipsen, Paris, France) of patients. Dose was increased during follow-up in 14% of cases starting at lower dose; in no case was it decreased. SSA was discontinued for more than 1 month in only 3.6% of patients. In both cohorts, approximately half of participants received Lanreotide Autogel and the other half octreotide long-acting release as SSA treatment.

Outcomes

Three-hundred progression events were recorded in the R-GETNE training cohort, with a median follow-up of 33.1 months in patients who did not experience progression (95% CI, 30.1 to 36.3 months). Median PFS and OS were 28.7 months (95% CI, 23.8 to 31.1 months) and 85.9 months (95% CI, 71.5 to 96.7 months), respectively. Curves for both PFS and OS in the R-GETNE cohort have been incorporated into the Data Supplement. Fifty progression events were detected in the external validation series, with median follow-up and PFS values of 31.5 months (95% CI, 15.9 to 41.9 months) and 29.0 months (95% CI, 20.9 to 50.1 months), respectively. Median OS was not reached.

Development of a Predictive Model of PFS

Both the NLR and Ki-67 percentage index had a pronounced time-varying effect that rapidly faded over time. The hazard ratio surface and the corresponding contour map for Ki-67 percentage are illustrated in Figures 1A and 1B. In the case of Ki-67 percentage, the effect was clearly nonlinear ($P = .030$) and found to be the predictor that correlated most closely with PFS (Somers' Dxy rank correlations in the Data Supplement). For example, the model illustrates that the residual effect of a Ki-67 percentage of 20% after 20 months of follow-up is approximately equivalent to the effect of a Ki-67 percentage of 7% evaluated at time zero, which must be determined if we are to clarify the true effect of Ki-67 percentage as a predictor of PFS. In contrast, no clear evidence of nonlinearity was detected for NLR (Figs 1C and 1D; $P = .420$).

The log-normal parametric survival time model adequately fitted the data to the most relevant prognostic factors (Data Supplement). Nine covariates were significantly associated with PFS: primary tumor site, Ki-67 percentage, NLR, alkaline phosphatase, percentage of hepatic tumor load, presence of bone and peritoneal metastases, documented progression status, and presence of symptoms at the time of the initiation of SSA therapy. No redundancy or interaction between covariates was detected.

Estimated PFS time ratios are listed in Table 2 and shown in Figure 2. An increase in Ki-67 percentage from 2% to 8% decreased median PFS by 36% (95% CI, 18% to 49%). The GETNE-TRASGU model had an adequate calibration (Fig 3A) and fair discrimination ability with a C-index of 0.714 (95% CI, 0.680 to 0.747) in the R-GETNE training cohort. The final model is graphically represented in a nomogram (Fig 4) and a Web-based calculator has been designed (http://www.iricom.es/prognostictools/trasgu). The underlying equation and example of its use are specified in

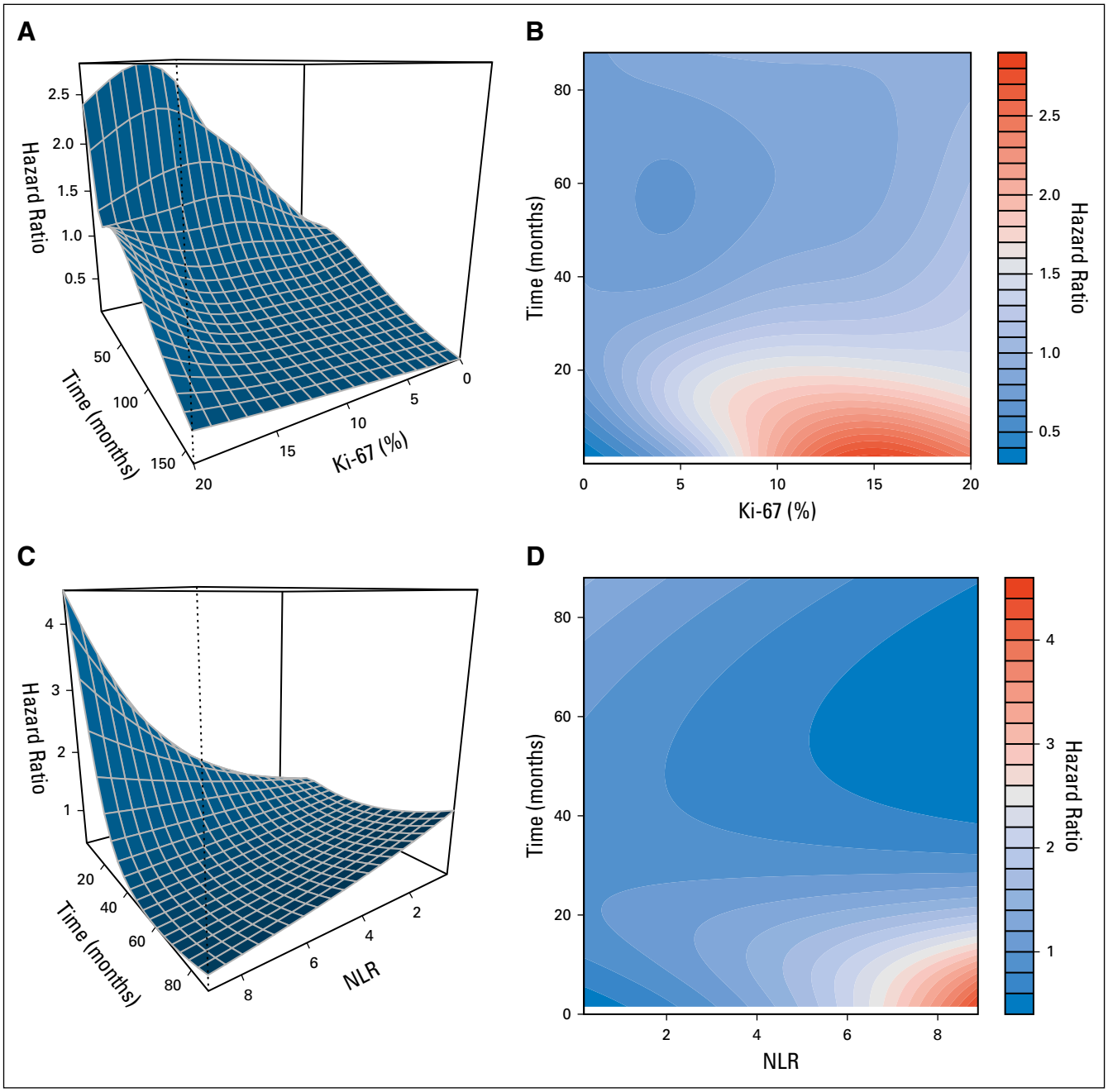

FIG 1. Three-dimensional surface and contour map showing the time-varying effects of Ki-67 percentage and neutrophil-to-lymphocyte ratio (NLR). (A) Three-dimensional surface plot showing the relation between Ki-67 percentage and time on the y- and x-axes, respectively. The z-axis shows the contribution of each combination on the hazard ratio for progression-free survival. (B) Contour map that uses a color gradient to visualize the effect of the combination on the hazard ratio, where the darker shades of blue indicate a decrease and the darker shades of red denote an increase on the hazard ratio. (C) Three-dimensional surface for NLR. (D) NLR contour map. The plot shows how the prognostic effect of Ki-67 percentage and NLR is diluted if the patient survives long enough without experiencing tumor progression. The nonlinear effect consists of higher levels of Ki-67 percentage being associated with a higher risk of progression, although there is a maximum level around 15% at which subsequent increases no longer correlate with greater risk. In contrast, NLR has a time-varying effect, but in this case the relation with hazard ratio is approximately linear.

the Data Supplement. The model is capable of capturing a remarkable prognostic heterogeneity, stratifying patients according to their risk (Data Supplement).

External Validation

The GETNE-TRASGU nomogram was validated in an independent series. In this external validation cohort, the model retained adequate calibration (Fig 3B) and continued to enable prognosis-based discrimination of patients with a C-index of 0.732 (95% CI, 0.658 to 0.806). Kaplan-Meier curves stratified on the basis of 2-year PFS predictions are presented in the Data Supplement.

TABLE 2. AFT Model to Predict Progression-Free Survival

AFT Model to Predict Progression-Free Survival	TR (95% CI)	*P*
Ki-67, 8% *v* 2%	0.64 (0.51 to 0.82)	< .001
NLR, 2 *v* 8	1.45 (1.04 to 2.00)	.026
Primary tumor site		
Pancreas, gastric	Ref	—
Small intestine	1.89 (1.45 to 2.46)	< .001
Unknown	1.39 (0.95 to 2.04)	.088
Colorectal	1.30 (0.88 to 1.91)	.174
Hepatic tumor burden, %		
No liver metastases	Ref	—
> 0-24	0.88 (0.64 to 1.21)	.451
25-50	0.67 (0.49 to 0.92)	.013
> 50	0.54 (0.37 to 0.78)	.001
Peritoneal metastases	0.63 (0.47 to 0.84)	.002
Bone metastases	0.63 (0.43 to 0.90)	.013
Alkaline phosphatase		
Normal	Ref	—
1.1-2.5 ULN	0.84 (0.64 to 1.09)	.200
> 2.5 ULN	0.61 (0.41 to 0.91)	.015
Documented progression status before SSA		
Tumor progression	Ref	—
Stable disease < 3 months or not documented	1.15 (0.91 to 1.44)	.224
Stable disease for ≥ 3 months	1.65 (1.10 to 2.49)	.015
Symptoms, asymptomatic	1.57 (1.18 to 2.10)	.001

NOTE. Interpretation of adjusted TRs: TR > 1 means that an increase in the value of the covariate is associated with longer survival; TR < 1 means that an increase in the value of the covariate is associated with shorter survival. Adjusted TRs are derived from a multivariable log-normal AFT model and represent its exponentiated coefficients.

Abbreviations: AFT, accelerated failure time; NLR, neutrophil-to-lymphocyte ratio; Ref, reference; SSA, somatostatin analog; TR, time ratio; ULN, upper limit of normal.

DISCUSSION

The current study describes the development and independent validation of the GETNE-TRASGU PFS prediction tool for its use in individuals diagnosed with advanced, well-differentiated GEP-NETs starting treatment with SSA. With 536 patients, it is the largest series published to date with this objective. To our knowledge, GETNE-TRASGU is the first statistical model to stratify and make individualized predictions regarding the prognosis of patients with NETs being treated with SSAs.[9,10] The model has been independently validated in an external validation sample of consecutive patients, maintaining an adequate calibration and capacity to discriminate PFS.

Two of the applicability criteria are particularly noteworthy: the absence of metastases that can potentially be cured with surgery or locoregional therapies and the presence of a Ki-67 percentage index of 20% or less. The GETNE-TRASGU model assigns an estimation of PFS on the basis of the additive effect of clinical, analytical, and pathologic variables. All variables included in this nomogram have been studied previously in GEP-NETs and have a well-known biologic substrate. They are all established prognostic factors; however, their predictive ability has not been described before.[9]

In the phase III PROMID study, median PFS ranged from 4.6 months to 29.4 months, depending on the extent of liver involvement.[8] Likewise, in the phase III CLARINET trial, midgut, hindgut, and pancreatic NETs that were treated with SSA behaved differently, with median PFS of 61.5 months, 55.0 months, and 29.7 months, respectively.[7,9] Documented disease progression status before SSA was a controlled variable in the CLARINET study, which attributed part of the favorable PFS to the fact that 96% of patients had stable disease at the time of inclusion.[9] In an observational study, Laskaratos et al[10] reported that the antiproliferative effect of SSAs depended on the location and histologic differentiation of the primary tumor. Both alkaline phosphatase and NLR have been correlated with OS in some series of NETs and general tumors.[32-34] The presence of bone metastases is associated with a poor prognosis in NETs and other neoplasms.[35] In the GETNE-TRASGU model, after controlling for multiple confounding factors, peritoneal involvement diminished PFS with a TR of 0.63 (95% CI, 0.43 to 0.90). In other series, such an adverse impact has not been explicitly reported, although there might be a relationship between peritoneal metastases and NETs that originate from the ileum or from the appendix, thus confounding those findings.[36] The functioning status variable has a highly complex meaning, as it may correlate with both high tumor burden and histologic differentiation. Although the previous series exhibited variable results overall, once Ki-67 percentage and tumor burden were controlled for and, above all, insulinomas excluded, available data did not corroborate functionality itself as having a favorable effect in this patient

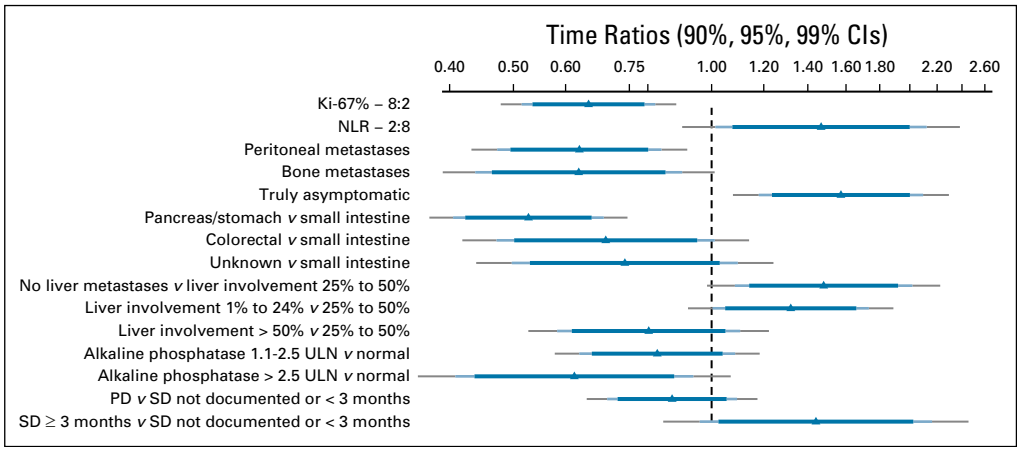

FIG 2. Effect of GETNE-TRASGU (Spanish Group of Neuroendocrine and Endocrine Tumors–Treated With Analog of Somatostatin in Gastroenteropancreatic and Unknown Primary Neuroendocrine Tumors) covariates on progression-free survival. Adjusted time ratios are derived from a multivariable log-normal accelerated failure time model and represent its exponentiated coefficients (Table 2). Interpretation of the adjusted time ratios (TR): TR > 1 means that an increase in the value of the covariate is associated with longer survival. TR < 1 means that an increase in the value of the covariate is associated with shorter survival. NLR, neutrophil-to-lymphocyte ratio; PD, progressive disease; SD, stable disease; ULN, upper limit of normal.

population.[37] In the GETNE-TRASGU study, the presence of both tumor and endocrine symptoms was associated with a similarly higher risk of disease progression.

In the GETNE-TRASGU study, we chose an AFT model with log-normal distribution, as opposed to the more usual proportional hazards model. The rationale for this choice is based on the fact that the Ki-67 percentage effect was the most heavily weighted variable; however, its importance gradually faded with prolonged follow-up. Slow growth exhibited by well-differentiated GEP-NETs that were treated with SSA—with expectations of PFS sometimes exceeding 60 months—suggests that the decreasing magnitude of impact of Ki-67 percentage on PFS, as observed here, likely occurs in other series.[7] Consequently, these dynamic effects should not be dismissed. Our data show that the formal verification of the assumption of proportionality of the hazard ratios is essential when studying NETs. In contrast, analysis of the nonlinear effect of Ki-67 percentage indicates that the cutoffs typically applied in the WHO classification are not compatible with the structure of these data. Analysis of the categorized histologic grade therefore entails a substantial loss of information.[2] In fact, categorizing the Ki-67 percentage by cutoffs has no known biologic basis. As a result, it must clearly be evaluated as a continuous variable that allows for nonlinear effects.

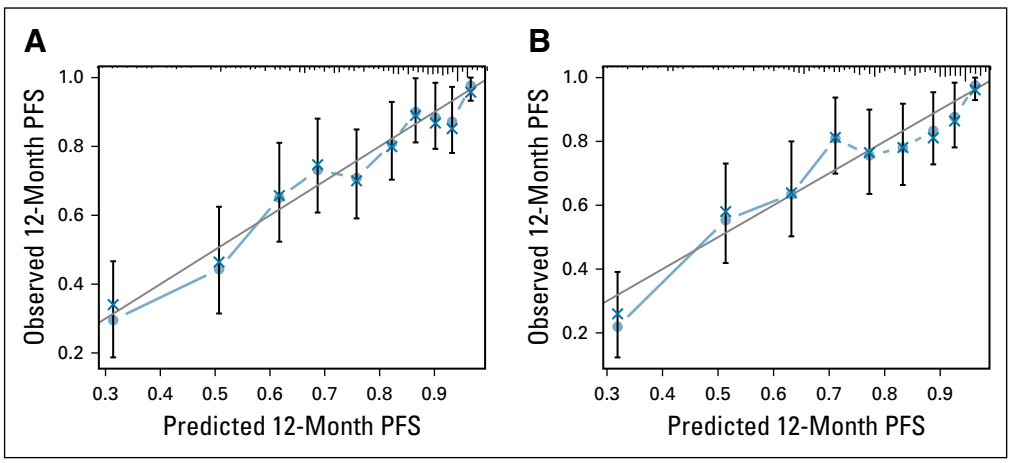

FIG 3. Calibration curves in the training and validation cohorts. (A) GETNE-TRASGU cohort. (B) Christie Hospital cohort. Calibration method consisted of obtaining estimates at intervals of the observed values versus model-predicted values. The term predicted means the probability of progression-free survival (PFS) at a fixed point of time, whereas observed refers to the Kaplan-Meier survival estimate stratified by intervals.

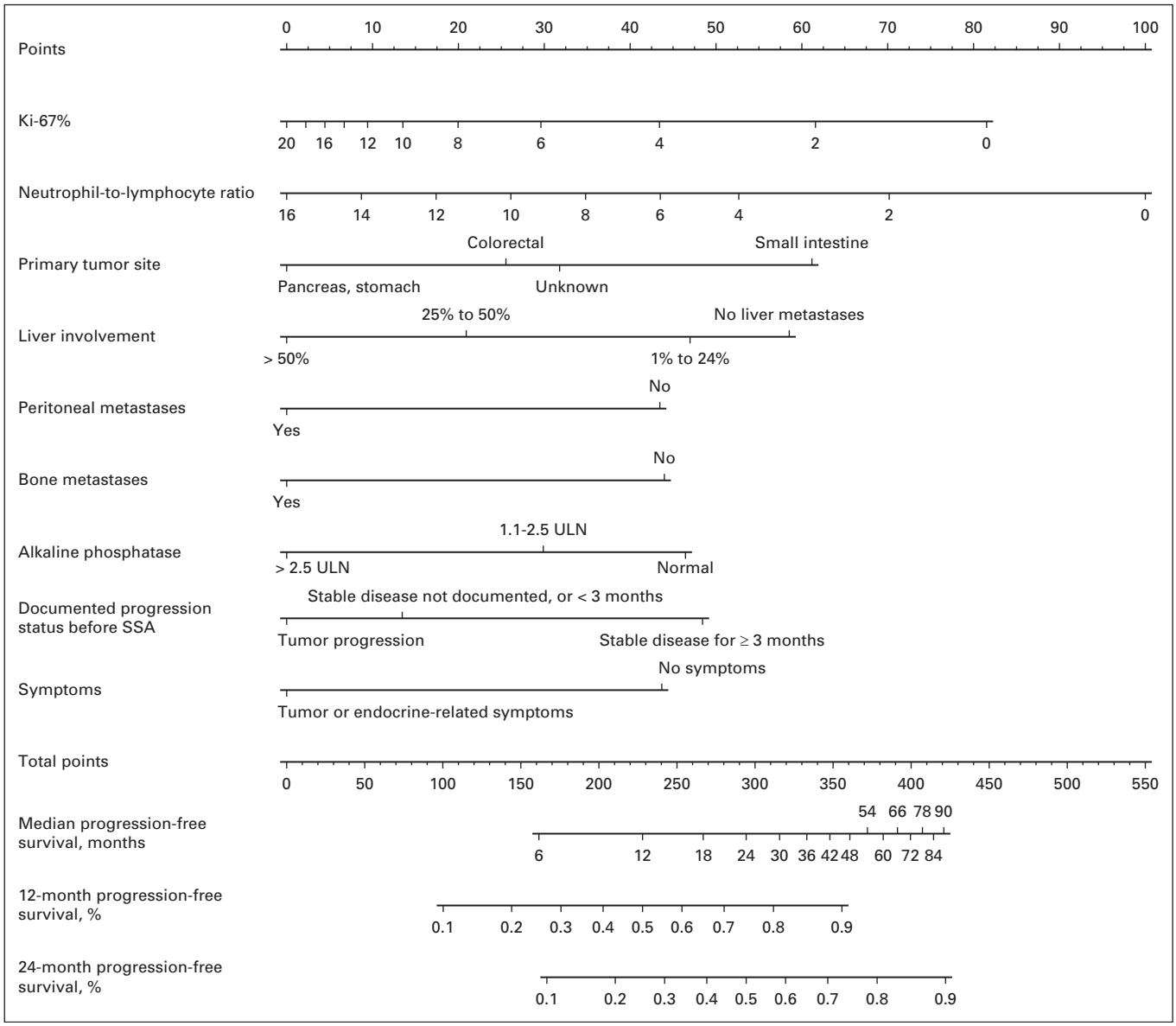

FIG 4. GETNE-TRASGU (Spanish Group of Neuroendocrine and Endocrine Tumors–Treated With Analog of Somatostatin in Gastroenteropancreatic and Unknown Primary Neuroendocrine Tumors) nomogram. SSA, somatostatin analog; ULN, upper limit of normal.

Some limitations to the GETNE-TRASGU study should be noted. First, it is based on retrospective data, with the consequent loss of accuracy that this entails. To diminish the negative impact of its retrospective design, we requested that researchers confirm the quality of the data by monitoring any possible inconsistency. Second, the chosen end point—researcher-defined PFS—may vary from centrally reviewed RECIST v1.1-defined PFS reported in prospective randomized studies.[10] We could argue the appropriateness of the chosen end point with the following. First, there are well-known limitations of RECIST for GEP-NETs.[38] In addition, researcher-defined PFS may reflect a more clinically relevant definition of progression to treatment with the inclusion of information on the need for alternative therapeutic strategy. The reader must also be aware that, as prognosis for patients with well-differentiated NETs is quantified in several years, the number of events is low, which makes the OS data more uncertain in the long term. Consequently, estimations entail greater uncertainty on the curve tails. Insofar as interpretation is concerned, it must be remembered that the model does not make a one-off prediction of what will happen to a given patient at a given point in time, but rather it establishes an estimation of a covariate-adjusted survival function. Inclusion of the proposed model as a key stratification factor in future clinical trials is strongly encouraged for a definitive prospective validation.

In conclusion, the GETNE-TRASGU nomogram is an evidence-based tool that is based on nine clinical variables

that make it possible to stratify patients with advanced GEP-NETs according to PFS estimated during SSA treatment. The GETNE-TRASGU tool can contribute to making treatment decisions in the individualized management of GEP-NETs and to provide risk stratification in future clinical trials with SSA.

AFFILIATIONS

[1]Hospital Universitario Morales Meseguer, Universidad de Murcia, Instituto Murciano de Investigación Biosanitaria, Murcia, Spain
[2]Hospital Universitario Central de Asturias, Oviedo, Spain
[3]The Christie NHS Foundation Trust, Manchester, United Kingdom
[4]University of Manchester, Manchester, United Kingdom
[5]Hospital Universitario de Fuenlabrada, Madrid, Spain
[6]Hospital Universitario Virgen del Rocío, Instituto de Biomedicina de Sevilla, Sevilla, Spain
[7]Hospital Universitario Miguel Servet, Zaragoza, Spain
[8]Hospital Universitario Doce de Octubre, Madrid, Spain
[9]Hospital Universitario Ramón y Cajal, Madrid, Spain
[10]Hospital Universitario La Paz, Centro de Investigación Biomédica en Red Cáncer, CB16/12/00398, Madrid, Spain
[11]Hospital Universitario Vall d'Hebron, Vall Hebron Institute of Oncology, Autonomous University of Barcelona, Barcelona, Spain
[12]Hospital Universitario Marqués de Valdecilla, Santander, Spain
[13]Hospital Universitario Donostia, San Sebastián, Spain
[14]Complexo Hospitalario Universitario de Ourense, Orense, Spain
[15]Hospital Universitario de la Princesa, Madrid, Spain
[16]Complejo Asistencial Universitario de Burgos, Burgos, Spain
[17]Hospital Clínico Universitario Lozano Blesa, Zaragoza, Spain
[18]Hospital Universitario Clínico San Carlos, Madrid, Spain
[19]Hospital Universitario Santa Lucia, Cartagena, Spain
[20]Hospital General Universitario de Elche, Elche, Spain
[21]Hospital Universitario de Canarias, Universidad de La Laguna, Tenerife, Spain
[22]Hospital Universitario La Fe, Valencia, Spain
[23]Hospital Universitari Arnau de Vilanova, Lleida, Spain
[24]Hospital Universitario Gregorio Marañón, Madrid, Spain
[25]MD Anderson Cancer Center Madrid, Madrid, Spain
[26]Hospital Universitario Doce de Octubre, Universidad Complutense de Madrid, Centro Nacional de Investigaciones Oncológicas, Centro de Investigación Biomédica en Red Cáncer, Madrid, Spain

CORRESPONDING AUTHOR

Alberto Carmona-Bayonas, MD, PhD, Hematology and Medical Oncology Department, Hospital Universitario Morales Meseguer, Universidad de Murcia, Instituto Murciano de Investigación Biosanitaria, Avenida Marqués de los Vélez, 30007, Murcia, Spain; Twitter: @crh_MoralesIMIB; @GrupoGetne; e-mail: alberto.carmonabayonas@gmail.com.

EQUAL CONTRIBUTION

A.C.-B. and P.J.-F. contributed equally to this work.

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AUTHOR CONTRIBUTIONS

Conception and design: Alberto Carmona-Bayonas, Paula Jiménez-Fonseca, Guillermo Crespo, Pilar Escudero, José Ángel Diaz, Juan Carlos Percovich, Enrique Grande, Rocío García-Carbonero

Administrative support: Paula Jiménez-Fonseca

Provision of study material or patients: Alberto Carmona-Bayonas, Paula Jiménez-Fonseca, Ángela Lamarca, Jorge Barriuso, Marta Benavent, Vicente Alonso, Teresa Alonso-Gordoa, Ana Custodio, Ana Fernández Montes, Pilar Escudero, Eduardo Feliciangeli, Felip Vilardell, Juan Carlos Percovich, Jaume Capdevila, Juan W. Valle, Rocío García-Carbonero

Collection and assembly of data: Alberto Carmona-Bayonas, Paula Jiménez-Fonseca, Ángela Lamarca, Jorge Barriuso, Ángel Castaño, Marta Benavent, Vicente Alonso, Teresa Alonso-Gordoa, Ana Custodio, Manuel Sánchez-Cánovas, Jorge Hernando Cubero, Carlos López, Adelaida Lacasta, Ana Fernández Montes, Mónica Marazuela, Guillermo Crespo, Pilar Escudero, José Ángel Diaz, Eduardo Feliciangeli, Javier Gallego, Marta Llanos, Ángel Segura, Felip Vilardell, Juan Carlos Percovich, Jaume Capdevila, Rocío García-Carbonero

Data analysis and interpretation: Alberto Carmona-Bayonas, Paula Jiménez-Fonseca, Ángela Lamarca, Jorge Barriuso, Vicente Alonso, María del Carmen Riesco-Martínez, Ana Custodio, Guillermo Crespo, José Ángel Diaz, Juan Carlos Percovich, Enrique Grande, Jaume Capdevila, Juan W. Valle, Rocío García-Carbonero

Manuscript writing: All authors

Final approval of manuscript: All authors

Accountable for all aspects of the work: All authors

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3. Carmona-Bayonas A, Jiménez-Fonseca P, Custodio A, et al: Optimizing somatostatin analog use in well or moderately differentiated gastroenteropancreatic neuroendocrine tumors. Curr Oncol Rep 19:72, 2017
4. Jiménez-Fonseca P, Carmona-Bayonas A, Martín-Pérez E, et al: Health-related quality of life in well-differentiated metastatic gastroenteropancreatic neuroendocrine tumors. Cancer Metastasis Rev 34:381-400, 2015
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6. Garcia-Carbonero R, Garcia-Figueiras R, Carmona-Bayonas A, et al: Imaging approaches to assess the therapeutic response of gastroenteropancreatic neuroendocrine tumors (GEP-NETs): Current perspectives and future trends of an exciting field in development. Cancer Metastasis Rev 34:823-842, 2015
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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Prediction of Progression-Free Survival in Patients With Advanced, Well-Differentiated, Neuroendocrine Tumors Being Treated With a Somatostatin Analog: The GETNE-TRASGU Study

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Alberto Carmona-Bayonas
Consulting or Advisory Role: Pfizer, Genentech
Speakers' Bureau: Rovi
Research Funding: LEO Pharma (Inst)
Travel, Accommodations, Expenses: Ipsen, Genentech, Novartis

Paula Jiménez-Fonseca
Other Relationship: Ipsen

Ángela Lamarca
Honoraria: Eisai, Nutricia, Nutricia (I)
Speakers' Bureau: Merck, Ipsen, Ipsen (I), Pfizer, Pfizer (I), Novartis (I), Incyte
Research Funding: Ipsen, Ipsen (I)
Travel, Accommodations, Expenses: Abbott Nutrition, Ipsen, Pfizer, Celgene, Novartis, Advanced Accelerator Applications, Sirtex Medical, Bayer, Ipsen (I), Delcath Systems, Mylan, NanoString Technologies (I)

Jorge Barriuso
Consulting or Advisory Role: Nutricia, Nutricia (I), Eisai (I)
Speakers' Bureau: Ipsen (I), Pfizer (I), Merck Serono (I), Pfizer, Novartis
Research Funding: Pfizer
Travel, Accommodations, Expenses: Advanced Accelerator Applications, Ipsen, Novartis, NanoString Technologies, Ipsen (I), Pfizer (I), Novartis (I), Bayer (I), Mylan (I), Advanced Accelerator Applications (I), Celgene (I), Pfizer

Marta Benavent
Consulting or Advisory Role: Pfizer, Ipsen
Travel, Accommodations, Expenses: Pfizer, Ipsen, Novartis

Vicente Alonso
Consulting or Advisory Role: Roche, Merck Serono, Amgen, Sanofi, Regeneron, Bayer, Novartis, Ipsen, Servier
Travel, Accommodations, Expenses: Merck Serono, Roche, Novartis, Amgen, Sanofi, Regeneron

Teresa Alonso-Gordoa
Consulting or Advisory Role: Ipsen, Pfizer, Novartis, Roche, Bristol-Myers Squibb, Sanofi, Janssen-Cilag, Astellas Pharma, AstraZeneca
Research Funding: Roche
Travel, Accommodations, Expenses: Pfizer, Sanofi

Manuel Sánchez Cánovas
Consulting or Advisory Role: KyowaKirin
Research Funding: Leo Pharma (Inst)
Travel, Accommodations, Expenses: MSD Oncology, Sanofi, Servier, LEO Pharma, Sanofi
Other Relationship: KyowaKirin, Mylan, Angelini Pharma, Sanofi, Rovi

Jorge Hernando Cubero
Speakers' Bureau: Eisai, Ipsen, Roche, Angelini Pharma
Travel, Accommodations, Expenses: Ipsen, Novartis, Advanced Accelerator Applications, Roche, AstraZeneca, Eisai

Carlos López
Honoraria: Roche, Merck, Sanofi, Novartis, Pfizer, Eisai, Ipsen, Bayer, AstraZeneca, Servier
Consulting or Advisory Role: Amgen, Roche, Sanofi, Merck, Servier, Pfizer, Ipsen, Bayer, Eisai
Research Funding: Amgen, Roche, Merck, Merck Sharp & Dohme, AstraZeneca, Sanofi, Bayer, Ipsen, Eisai, Celgene
Travel, Accommodations, Expenses: Roche, Pfizer, Merck, Servier, Amgen, Ipsen

Adelaida Lacasta
Travel, Accommodations, Expenses: Amgen, Roche, Ipsen

Ana Fernández Montes
Consulting or Advisory Role: Sanofi, Amgen
Speakers' Bureau: Sanofi, Roche, Servier, Eli Lilly, Celgene

Mónica Marazuela
Consulting or Advisory Role: Novartis, Ipsen, Pfizer
Speakers' Bureau: Novartis, Ipsen, Pfizer

Guillermo Crespo
Consulting or Advisory Role: Pfizer, Bristol-Myers Squibb, Ipsen, Roche, MSD, Eisai, Sanofi, Novartis, Janssen, Bayer, Astellas Pharma
Travel, Accommodations, Expenses: MSD, Ipsen

José Ángel Diaz
Consulting or Advisory Role: Ipsen, Merck, Roche, Merck Serono, MSD, Servier

Eduardo Feliciangeli
Honoraria: Astellas Pharma
Consulting or Advisory Role: Merck Serono
Travel, Accommodations, Expenses: Roche, MSD Oncology, Servier, Pfizer, Merck Serono

Javier Gallego
Consulting or Advisory Role: Amgen, Bayer, Roche, Bristol-Myers Squibb, Celgene
Speakers' Bureau: Amgen, Ipsen, Eli Lilly
Travel, Accommodations, Expenses: Amgen, Novartis

Marta Llanos
Honoraria: Servier, Roche, Bristol-Myers Squibb, Ipsen, Sanofi, Eisai, Eli Lilly
Consulting or Advisory Role: Amgen

Juan Carlos Percovich
Honoraria: Pfizer, Novartis, Ipsen, Novo Nordisk, Sanofi

Enrique Grande
Honoraria: Pfizer, Bristol-Myers Squibb, Ipsen, Roche, Eisai, Eusa Pharma, MSD, Genzyme, Adacap, Novartis, Pierre Fabre, Lexicon, Celgene, Janssen-Cilag, Astellas Pharma
Consulting or Advisory Role: MSD, Pfizer, Ipsen
Research Funding: MTEM/Threshold (Inst), Roche, Pfizer (Inst), AstraZeneca (Inst), Ipsen (Inst)
Travel, Accommodations, Expenses: Bristol-Myers Squibb, Genentech, Pfizer, Janssen-Cilag

Jaume Capdevila
Consulting or Advisory Role: Bayer, Eisai, Sanofi, Exelixis, Novartis, Ipsen, Pfizer, Merck Serono, Advanced Accelerator Applications
Speakers' Bureau: Bayer, Eisai, Sanofi, Novartis, Ipsen, Pfizer, Merck Serono
Research Funding: Eisai (Inst), AstraZeneca (Inst), Advanced Accelerator Applications (Inst), Novartis (Inst), Ipsen (Inst), Bayer (Inst), Pfizer (Inst)
Travel, Accommodations, Expenses: Pfizer, Ipsen, Eisai

Juan W. Valle
Honoraria: Ipsen
Consulting or Advisory Role: Ipsen, Novartis, AstraZeneca, Merck, Delcath Systems, Agios, Pfizer, PCI Biotech, Incyte, Keocyt, QED, Pieris Pharmaceuticals, Genoscience Pharma, Mundipharma, Wren Laboratories, NuCana BioMed
Speakers' Bureau: Novartis, Ipsen, Nucana, Imaging Equipment
Research Funding: Novartis (Inst)
Travel, Accommodations, Expenses: Celgene, Nucana, Pfizer

Rocío García-Carbonero
Honoraria: Ipsen, Roche, Sanofi, Bristol-Myers Squibb, Servier, Novartis, Pfizer, Merck, PharmaMar, Adacap, Merck (I), PharmaMar (I), Roche (I), Bristol-Myers Squibb (I), AstraZeneca (I), Eli Lilly (I), Boehringer Ingelheim (I), Gilead Sciences (I), Servier (I), Sysmex (I)
Consulting or Advisory Role: Ipsen, Novartis, Pfizer, Advanced Accelerator Applications
Speakers' Bureau: Ipsen, Pfizer
Research Funding: Pfizer (Inst), Bristol-Myers Squibb (Inst), MSD (Inst), AstraZeneca (Inst)
Travel, Accommodations, Expenses: Roche, Merck

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